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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S–151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ASGHAR, Aziz [GB/GB]; School of Biomedical Sciences, The Worsley Building, University of Leeds, Leeds LS2 9NQ (GB). CABERO, José, Luis [SE/SE]; Astra Hässle AB, S–431 83 Mölndal (SE). DRAY, Andrew [GB/CA]; Astra Research Centre Montreal, 7171 Frederick–Banting, St. Laurent, Quebec H4S 1Z9 (CA). KING, Anne [GB/GB]; School of Biomedical Services, The Worsley Building, University of Leeds, Leeds, LS2 9NQ (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S–151 85 Södertälje (SE).

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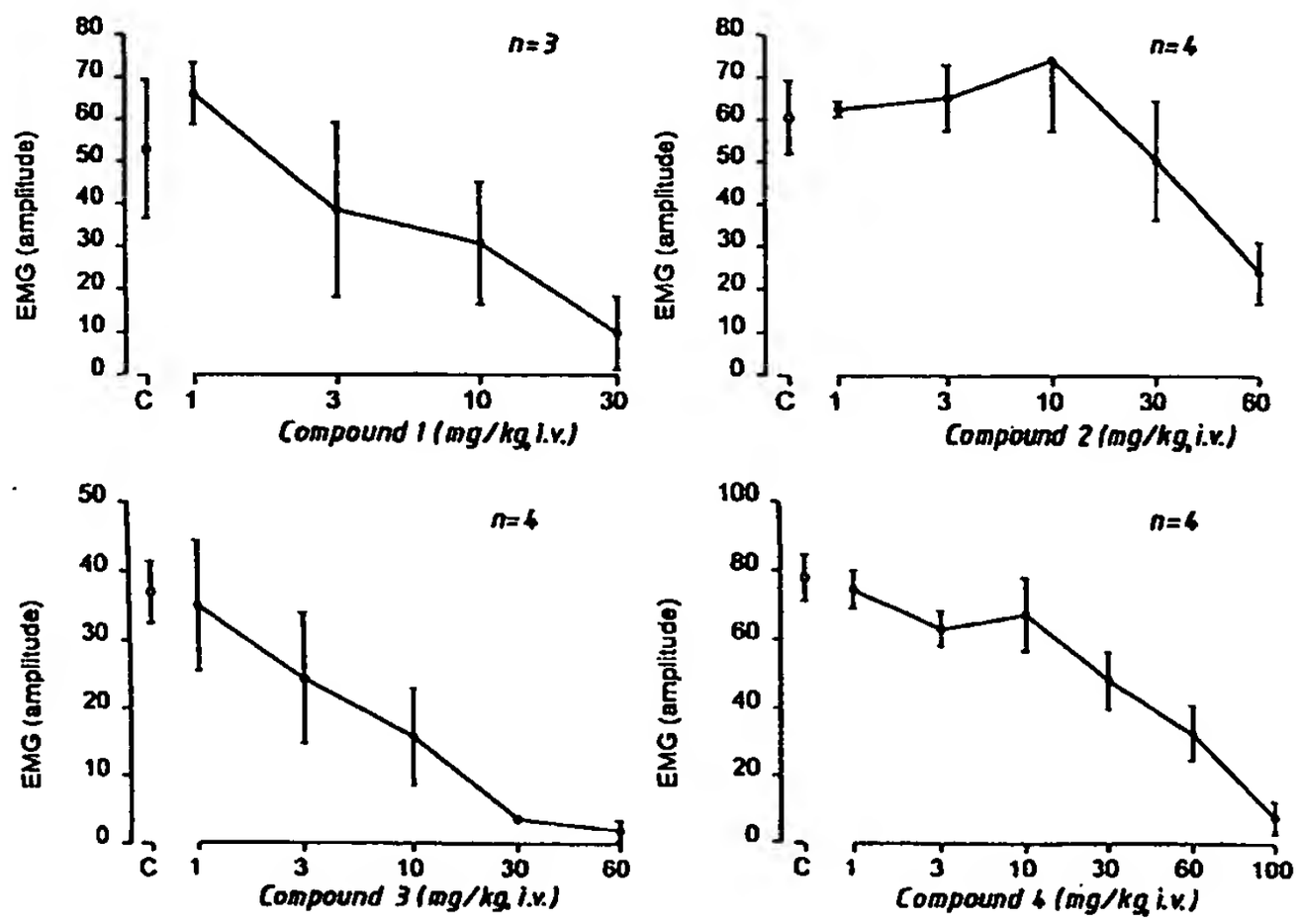

(57) Abstract

The invention relates to the use of pharmaceutical compounds having NMDA antagonist activity for treating certain conditions in the gastrointestinal tract, such as functional gastrointestinal disorders, and in particular irritable bowel syndrome (IBS). The invention also relates to pharmaceutical compositions to be used in the treatment of IBS and product comprising such compounds and a pharmaceutical acceptable carrier.

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USE OF NMDA ANTAGONISTS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME

Field of the invention

The present invention relates to the use of compounds having NMDA antagonist activity for treating certain conditions in the gastro intestinal tracts, such as functional gastrointestinal disorders, and in particular irritable bowel syndrome (IBS), where the condition known as visceral hypersensitivity may be a major contributory factor in the observed symptoms. The invention also relates to pharmaceutical compositions intended for the treatment of IBS.

Background of the invention

Compounds having NMDA (N-methyl-D-aspartate) antagonist activity are known in the art, for example see Watkins et al., Trends in Pharmacological Science, 11:25, 1990.

In particular certain compounds are disclosed in EP-A 279937 as having NMDA antagonist activity and are useful for treating various CNS disorders such as epilepsy and Parkinson's disease. In particular the compound known as remacemide is known from EP-A 279937 as an NMDA antagonist and has also been shown to act as a sodium channel antagonist (Wamil et al., Epilepsy Research 23:1. 1996). It has now surprisingly been found that antagonists of the NMDA receptor have an attenuating effect on the visceromotor response to colorectal distention in rats when dosed intravenously but not when dosed intrathecaly. This observation coupled with the observation that the compounds also show an attenuating effect in a model of pelvic nerve afferent activity, would suggest that the effect of these NMDA antagonists is dependant at least in part on a peripheral component. It does not however, rule out an additional action at the spinal or supra-spinal level, in the attenuation of the response to colorectal distension . As a result it is expected that compounds having NMDA antagonist activity which in some cases may be combined with sodium channel antagonist activity will be useful for the treatment of certain conditions in the gastro intestinal tracts where the phenomenon of visceral hypersensitivity may be involved, such as functional bowel disorders, and in particular irritable bowel syndrome.

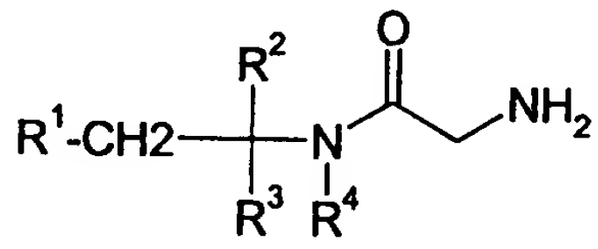
Suitable NMDA antagonists include those listed in WO 94/13295 such as a) channel blockers, i.e. antagonists which operate in an uncompetitive or non-competitive manner to block the NMDA receptor channel, b) receptor antagonists that compete with NMDA to act at the NMDA binding site, c) agents acting at either the glycine co-agonist site or any of the several modulation sites such as the zinc site, the magnesium site, the redox

modulatory site, or the polyamine site, d) agents which inhibit the downstream effects of NMDA receptor stimulation such as agents which inhibit the activation of protein kinase C activation by NMDA stimulation, antioxidants, and agents that decrease phosphatidylinositol metabolism.

The hypersensitive state, such as that which may occur in patients with functional bowel disorders, may occur as a result of excessive receptor activation. Hence, antagonists which operate in an uncompetitive or non-competitive manner, may offer an advantage as they can only block the receptor when it is in its activated state and not when it is in its non-activated form. Thus excess receptor activity will be curtailed.

Examples of preferred compounds useful for the invention include but are not limited to memantine (Merz) and remacemide and their metabolites

Particularly suitable compounds are those disclosed in EPA 279937, such as a compound of formula (I):



(I)

where:

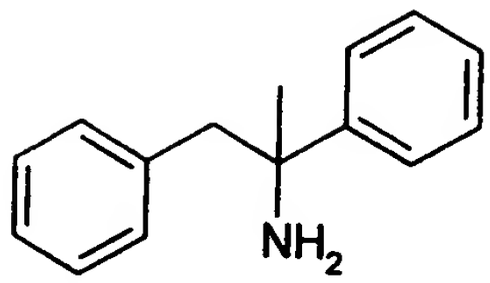
R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

R^4 is hydrogen or methyl;

and metabolites and isomers thereof both as free base and pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I) include 2-amino-N-(1,2-diphenyl-1-methylethyl)acetamide (remacemide) or a metabolite thereof, such as the compound 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof which has the following structure:



Other preferred compounds include those disclosed in WO 93/20052, in particular (S)-1-phenyl-2-(2-pyridyl)ethanamine as well as the compounds mentioned in the experimental section herein. Certain compounds mentioned herein are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these individual stereoisomeric forms and to any mixtures thereof including racemates. The invention also extends to any tautomeric forms of the compounds mentioned and mixtures thereof.

Suitable salts of the above noted compounds include all known pharmaceutically acceptable salts such as acid addition salts and preferably hydrochloride salts.

Compounds which possess anti-inflammatory properties are useful in the prevention of clinical hyperalgesia and other pathologies associated with chronic pain such as neuropathies and joint inflammation. Particular inflammatory disorders which can be treated include arthritic conditions, eczema, psoriasis, dermatitis and other inflammatory conditions such as sunburn; inflammatory eye conditions such as uveitis and conjunctivitis; lung disorders in which inflammation is involved such as asthma and bronchitis; conditions of the GI tract including aphthous ulcers, gingivitis, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional iletis, peptic ulceration, IBS, pyresis, pain, including inflammatory induced pain, and other damage to the GI tract, for example damage from infections by, for example, Helicobacter pylori, or undesirable side effects from treatments with non-steroidal anti-inflammatory drugs.

Outline of the invention

In a preferred embodiment it has been found that certain NMDA antagonists are expected to be useful for the treatment of certain conditions in the GI tract, in particular functional bowel disorders.

In a further aspect the invention therefore provides use of an NMDA antagonist for the treatment or prevention of irritable bowel syndrome (IBS). Suitable NMDA antagonists

include those listed above. In particular a preferred aspect of the invention relates to the use of non-competitive NMDA antagonists such as memantine for the treatment of IBS. Other preferred compounds for the treatment or prevention of IBS include remacemide, and also compounds of formula I, such as (S)-1-phenyl-2-(2-pyridyl)ethanamine, 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride, alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride.

In a preferred embodiment the invention provides a method of treating or preventing IBS which comprises administering to a patient in the need thereof a compound having NMDA antagonist activity or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound having NMDA antagonist activity in the manufacture of a medicament for use in the prevention or treatment of IBS, and a pharmaceutical composition comprising such a compound and a pharmaceutical acceptable carrier.

Other diseases which may be treated with the compounds of the invention include functional gastrointestinal disorders as defined by the Rome group in *"The Functional Gastrointestinal Disorders"*, D. Drossman ed., Little Brown & Co., 1994, p.p. 370. In particular: irritable bowel syndrome and functional dyspepsia (non-ulcer dyspepsia) but also functional chest pain of presumed oesophageal origin, functional heartburn, functional dysphagia, non-cardiac chest pain, symptomatic gastro-oesophageal disease, gastritis, aerophagia, functional constipation, functional diarrhea, burbulence, chronic functional abdominal pain, functional biliary pain, functional incontinence, functional ano-rectal pain, pelvic floor dyssenergia, un-specified functional ano-rectal disorder. Additional conditions include cholecystalgia, interstitial cystitis, dysmenorrhea, dyspareunia, cancer related pain, migraine, osteoarthritis and rheumatoid arthritis.

Use of the invention

Suitable daily dose ranges of the compound having NMDA antagonist activity are from about 1.0 mg/kg to about 100 mg/kg. Unit doses may be administered conventionally once or more than once a day, for example, 2, 3, or 4 times a day, more usually 1 or 2 times a day.

The following examples illustrate the invention.

Example 1

Effects of non-competitive NMDA glutamate receptor antagonists on the visceromotor response (VMR) elicited by colorectal distension (CRD)

Methods:

Animals

Adult male Sprague-Dawley rats (250-350g, Harlan, San Diego, CA) served as animal subjects. Rats were housed 5-6 per cage, allowed free access to food and water, and were maintained on a 12 h light-dark cycle (lights on between 06.00 and 18.00 h).

Surgical preparation

Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg, Nembutal, Abbott Labs, North Chicago, IL) administered intraperitoneally. Electrodes (Teflon coated stainless steel wire, Cooner Wire Sales, Chatworth, CA) were stitched into the external oblique musculature, just superior to the inguinal ligament, for electromyographic (EMG) recording. The electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. Some animals were also implanted with venous catheters in the femoral vein to enable i.v. administration of drugs. For intrathecal (i.t.) drug administration, an i.t. catheter (PE-10 tubing, 8.5 cm long) was inserted through the dura overlying the atlanto-occipital junction and threaded to the level of the lumbar enlargement (Yaksh and Rudy, 1976). The venous or i.t. catheter was surgically anchored to musculature at the back of the neck, and externalized with the electrode leads. The wounds were closed in layers with 4-0 silk. Rats were housed singly and allowed to recuperate for at least 3-5 days prior to testing.

Behavioral testing

The stimulus employed has been previously described (Gebhart and Sengupta, 1996). Briefly, the descending colon and rectum were distended by pressure-controlled air inflation of a 6 cm long flexible latex balloon tied around a flexible tube (Tygon). The balloon was lubricated (Surgilube, E. Fougera and Co., Melville, NY), inserted intra-anally

and anchored by taping the balloon catheter to the base of the tail. Noxious phasic CRD (80 mmHg, 20 s) was achieved with the aid of a device (developed in house at Astra Hässle.) Intracolonic pressure was continuously monitored on line. The behavioral response quantified was the visceromotor response, a contraction of the abdominal and hindlimb (Ness and Gebhart, 1988). EMG activity in the external oblique musculature was quantified by computing the average amplitude (Dr. Alfred Bayati Astra Hässle). Each distension trial lasted 60 s and EMG activity was quantified 20 s before distension (baseline), during distension, and 20 s after distension. The increase in EMG amplitude during distension over baseline was recorded as the response.

Experimental protocol

On the day of testing, animals were briefly anesthetized with Metophane®, and the balloon was inserted and secured in place as described above. Rats were allowed to recover for 30-40 min, following which two stable control responses to CRD (80 mmHg, 20 s, 4 min interstimulus interval) were obtained.

Drugs were administered i.v. into the femoral vein through the indwelling catheter. All doses were administered in a volume of up to 230 µl followed by a flush with 100 µl of preservative-free saline over a period of 30s. Dose response curves were generated using a cumulative dosing paradigm. The first i.v. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.

In one group of animals, memantine was administered to the lumbar enlargement through the indwelling i.t. catheter with the aid of a 16 gauge injection needle connected to a 25 µl Hamilton syringe by a length of polyethylene tubing (PE-10). All doses were administered in a volume of 5 µl followed by a flush with 10 µl of preservative-free saline over a period of 1 min. The progress of the injection was continuously monitored by following the movement of an air bubble in the tubing. The dose response curve was generated using a cumulative dosing paradigm. The first i.t. injection was made 2 min after the second control response. Subsequent doses were injected 8 min apart, thus allowing two distensions after each dose. Data are reported as the average response to the two distensions.

Drugs

Drugs used in the present study were memantine hydrochloride (Research Biochemicals International, Natick, MA), and 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride, alpha-phenyl-1H-pyrazolc-1-ethanamine hydrochloride, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride (Astra Arcus, Rochester, NY). Stock solutions were freshly prepared by dissolving the drugs in distilled water, and then diluted as needed.

Results:

All drugs administered i.v. produced a dose-dependent attenuation of the VMR to noxious CRD (80 mmHg) in naïve animals without producing any apparent motor effects. At the most effective dose tested, memantine (10 mg/kg) attenuated the VMR to 28 % of control, 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride (60 mg/kg) to 40 % of control, alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride (100 mg/kg) to 10 % of control, (+)-N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride (60 mg/kg) to 5 % of control and 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride to 13 % of control.

In contrast, memantine administered i.t. (1-100 nmol) was without effect in diminishing the VMR to CRD. This is supported by other studies wherein NMDA receptor antagonists administered i.t. were without effect on normal visceral nociceptive reflexes, except in doses that produce motor impairment (Rice and McMahon, 1994; Coutinho et al., 1996a; Ide et al., 1997).

These data suggest that memantine as well as the other open channel blockers tested may be interacting with peripheral NMDA receptors.

Therefore it appears that activity at peripheral NMDA receptors plays a role in modulating responses to CRD.

Results are presented in Figures 1 to 4, which figures show the following:

Fig 1. Illustrates the effect of intravenous (i.v.) administration of memantine hydrochloride on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. Memantine dose-dependantly attenuate VMR when given i.v. from 1-10 mg/kg.

Fig 2. Effect of intrathecal (i.t.) administration of memantine hydrochloride on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. Memantine did not attenuate VMR when given i.t. up to a dose of 100 nmol.

Fig 3. Effect of intravenous (i.v.) administration of four compounds on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. All four compounds dose-dependently (1-10 mg/kg) attenuated VMR.
Compound 1 is 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride
Compound 2 is 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride
Compound 3 is (+) N-ethyl-1-phenyl-2-(3-pyrazine)ethanamine hydrochloride
Compound 4 is alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride

Fig 4. Effect of intrathecal (i.t.) administration of three compounds on viscero-motor responses (VMR) to noxious colorectal distension of concious rats. None of the three compounds attenuated VMR up to a dose of 300nmol.
Compound 1 is 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine trihydrochloride
Compound 2 is 2-amino-N-(1,2-diphenylethyl)acetamide hydrochloride
Compound 4 is alpha-phenyl-1H-pyrazole-1-ethanamine hydrochloride

Example 2

Effects of non-competitive NMDA glutamate receptor antagonists on pelvic afferent nerve activity

General procedures: Male Sprague-Dawley rats 425-450 g) were anesthetized initially with sodium pentobarbital (40-45 mg/kg ip) and maintained with α-chloralose (60 mg kg^{-1} h^{-1}). The trachea was cannulated for mechanical ventilation with room air. The left common carotid artery was cannulated for recording blood pressure. The femoral artery and vein were catheterized for injection of drug and anesthetic, respectively. Rats were paralyzed with pancuronium bromide (0.3 mg/kg i.v.) and ventilated with room air (55-60 strokes/min and 3-4 ml stroke volume). Supplemental doses of pancuronium bromide (0.2-

0.3 mg kg^{-1} h^{-1}) were given to maintain paralysis during the course of experiment. The mean arterial blood pressure was monitored continuously and maintained at >80 mm Hg with supplemental intravenous injection of 5% dextrose in saline given in a bolus of 1 to 1.5 ml as required. The core body temperature was maintained at 36°C by a hot-water-circulating heating pad underneath the rat and a feedback-controlled heat lamp (thermoprobe inserted into the thoracic esophagus). At the end of an experiment, the rat was killed by an overdose of intravenous pentobarbital sodium.

Surgical procedure: The lower abdomen was exposed by a 3-4 cm long incision laterally at the left flank. The urinary bladder was emptied and catheterized (PE-100) through the fundus. The urethra was ligated close to its entry to the penis and urine was constantly evacuated via the fundic catheter.

The pelvic nerve was approached near the major pelvic ganglion and isolated. A pair of Teflon-coated stainless steel wires stripped at the tips were wrapped around the pelvic nerve and sealed with non-reactive Wacker gel. The hypogastric, pudendal, and femoral nerves were isolated and transected. The sciatic nerve was approached through the ischiatic notch and transected. The abdomen was closed with silk sutures.

The lumbosacral spinal cord was exposed by laminectomy (T_{13}-S_2) and the rat was suspended from thoracic vertebral and ischial spinal clamps. The dorsal skin was reflected laterally and tied to make a pool for mineral oil. The dura was carefully removed and the spinal cord was covered with warm (37°C) mineral oil. For colorectal distension (CRD), a 6 - 7-cm long, 2 - 3 cm diameter flaccid, flexible latex balloon was inserted into the descending colon and rectum as described above.

Recordings of afferent nerve action potentials: The S_1 dorsal root was identified and decentralized at its entry to the spinal cord. Recordings were made from the distal cut end of the central processes of primary afferent fibers. a length of nerve fiber was draped over a black micro-base plate immersed in warm (37°C) mineral oil. The dorsal rootlet was split into thin bundles and a fine filament was isolated from the bundle to obtain a single unit. Electrical activity of single units was recorded monopolarly by placing a teased fiber over one arm of a bipolar silver-silver chloride electrode; a fine strand of connective tissue was placed across the other pole of the electrode. Action potentials were monitored continuously by analog delay and displayed on a storage oscilloscope after initial amplification through a low-noise ac differential amplifier. Action potentials were processed through a window discriminator and the frequency of impulses were counted (1s binwidth) on-line using the spike2/ced 1401 data acquisition program. Peri-stimulus time

histograms (PSTH), urinary bladder or colonic distending pressures, and blood pressure were displayed on-line.

Experimental protocol: Pelvic nerve input to the s_1 dorsal root was identified first by electrical stimulation of the pelvic nerve (a single 0.5 ms square-wave pulse at 5-8 mA). The organ innervated was identified by response to phasic CRD (80mm Hg, 2-3s). If a fiber responded to CRD, a stimulus-response function to phasic distending pressures of 5, 10, 20, 30, 40, 60, 80, and 100 mm Hg, 30s each at 4 min intervals was determined.

The effect of the NMDA-antagonist, memantine, was tested on responses of mechanosensitive pelvic nerve afferents to 80 mm Hg of CRD. The drug was administered intra-arterially in a cumulative dose paradigm. Each dose of the drug was given 2 min before CRD. A cumulative dose-response relationship for memantine was obtained by giving 1, 3, 6 and 10 mg/kg.

Figure 5 shows the results for memantine and Figure 6 shows the corresponding results with 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine.

Results and conclusion: Intra-arterially injected memantine reduced, in a dose-dependent fashion, the pelvic nerve activity elicited by distention of the colon (80 mm Hg), as can be seen from Figure 5.

The observations hereby provided are consistant with a model in which the non-competitive NMDA-antagonist memantine reduces the pelvic nerve activity elicited by colorectal distention by a peripheral mechanism of action.

The data shown in Figure 6 was obtained when the experiment was repeated with 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine.

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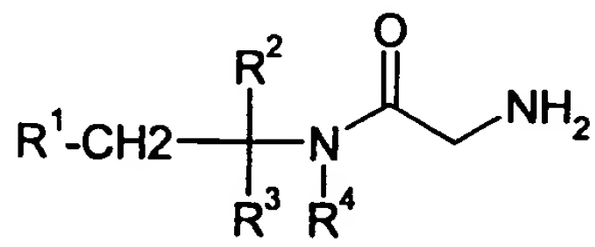
CLAIMS

1. Use a compound having NMDA antagonist activity in the manufacture of a medicament for the treatment of irritable bowel syndrome (IBS).

2. Use according to claim 1 wherein the compound having NMDA antagonist activity is a non-competitive NMDA antagonist.

3. Use according to claim 1 wherein the compound having NMDA antagonist activity is a compound of formula (I):



(I)

where:

R^1 and R^2 are independently phenyl or 4-fluorophenyl;

R^3 is hydrogen, C_{1-6} alkyl or methoxycarbonyl;

R^4 is hydrogen or methyl;

and metabolites and isomers thereof both as a free base and pharmaceutically acceptable salts thereof.

4. Use according to claim 3 wherein the compound of formula (I) is remacemide or a pharmaceutically acceptable salt thereof.

5. Use according to claim 3 wherein the compound is 2,3-diphenyl-2-propylamine or a pharmaceutically acceptable salt thereof.

6. Use according to claim 3 wherein the compound is (S)-1-phenyl-2-(2-pyridyl)ethanamine or a pharmaceutically acceptable salt thereof.

7. Use according to claim 1 wherein the NMDA antagonist is memantine or a pharmaceutically acceptable salt thereof.

8. Use according to claim 1 where the compound is 2-amino-N-(1,2-diphenylethyl)acetamide, alpha-phenyl-1H-pyrazole-1-ethanamine, (+)-N-ethyl-1-phenyl-

2-(3-pyrazine)ethanamine, or 2-amidino-6-(2-amino-2-phenyl)-ethylpyridine or a pharmaceutically acceptable salt thereof.

9. A method of treating or preventing irritable bowel syndrome which comprises administering to a patient in the need thereof a compound having NMDA antagonist activity or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for the treatment of irritable bowel syndrome comprising a compound having NMDA antagonist activity and a pharmaceutical acceptable carrier.

11. Pharmaceutical composition according to claim 10, wherein the compound having NMDA antagonist activity is a non-competitive NMDA antagonist.

12. Pharmaceutical composition according to claim 10, wherein the compound having NMDA antagonist activity is a compound of formula I defined in claim 3.

Fig. 1

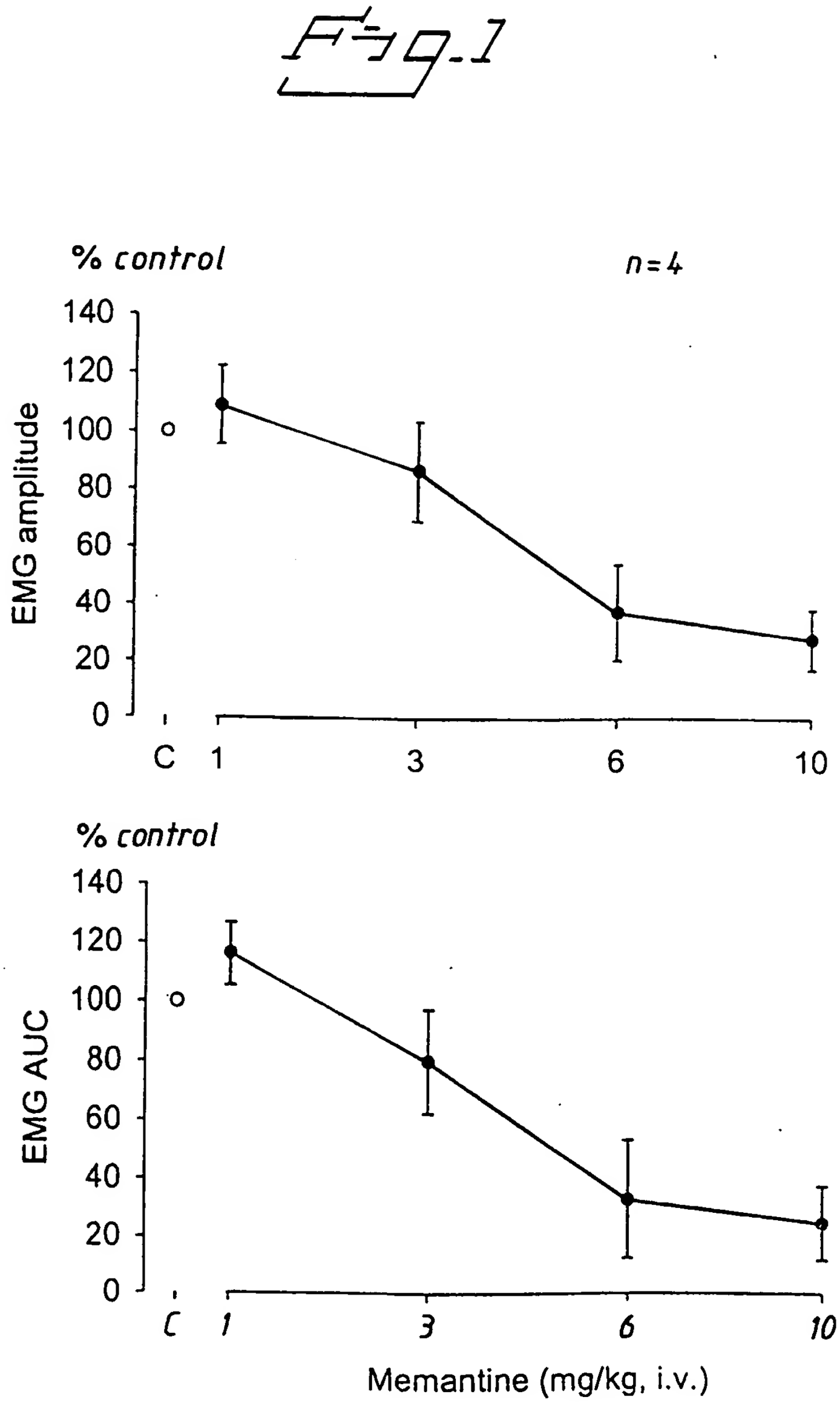
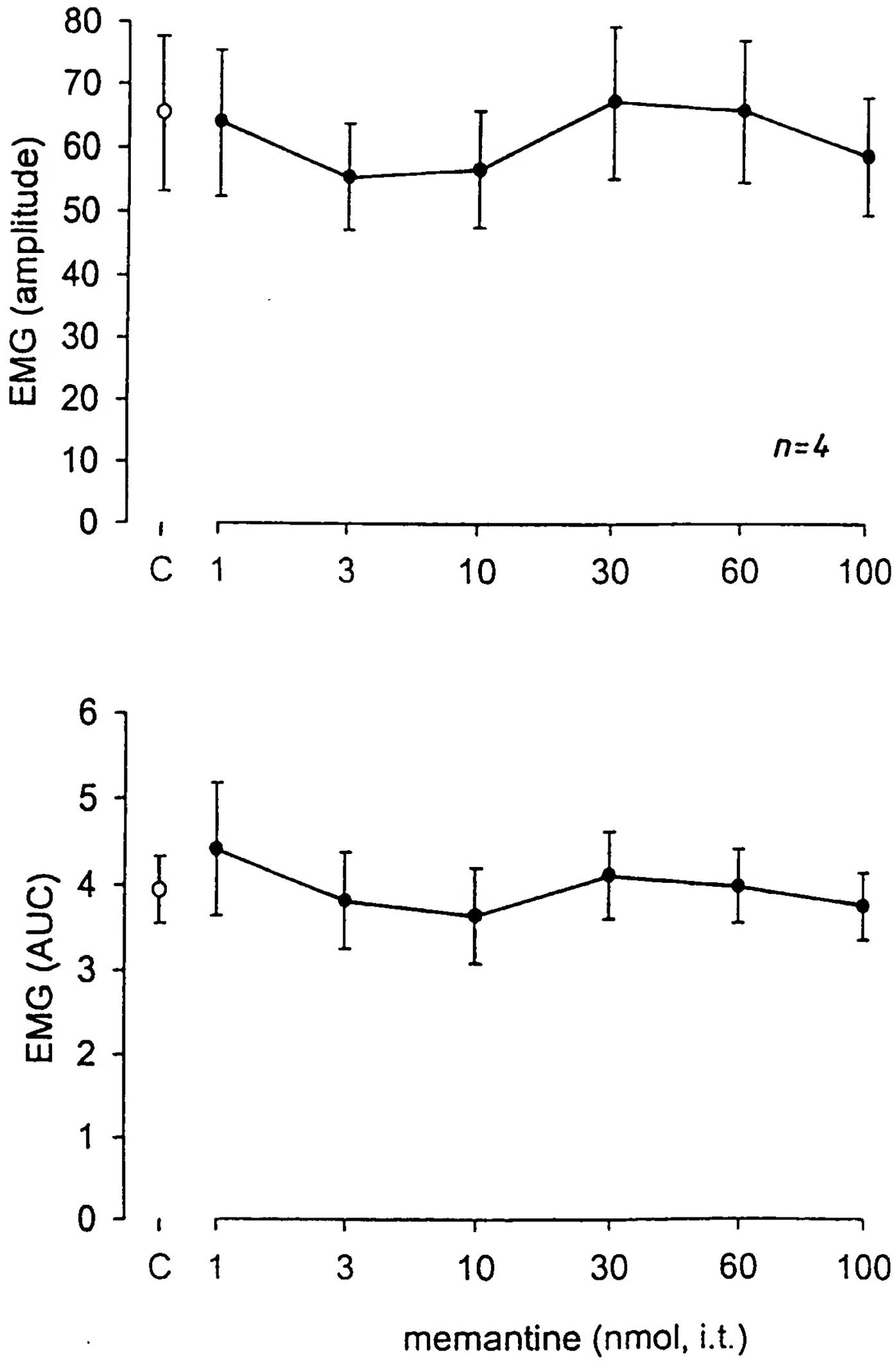
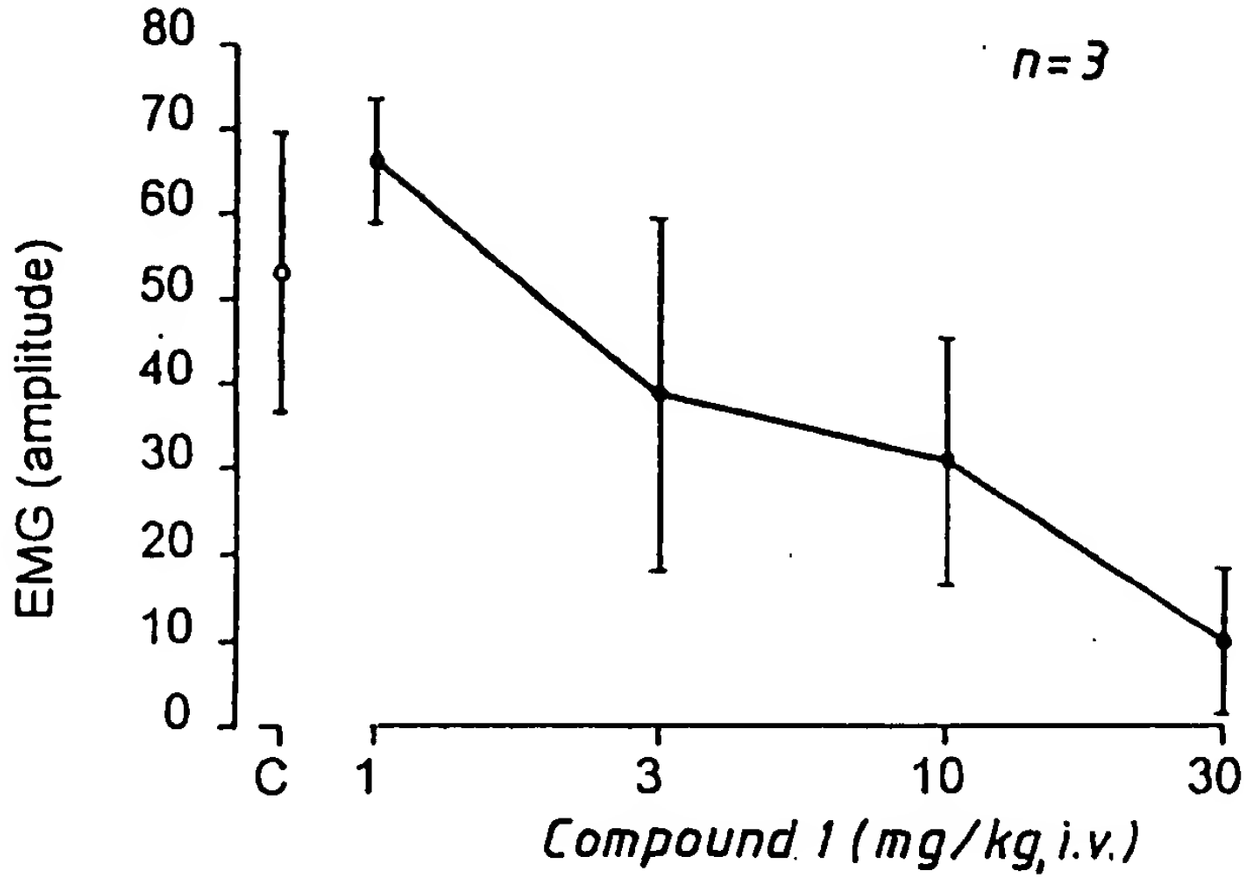
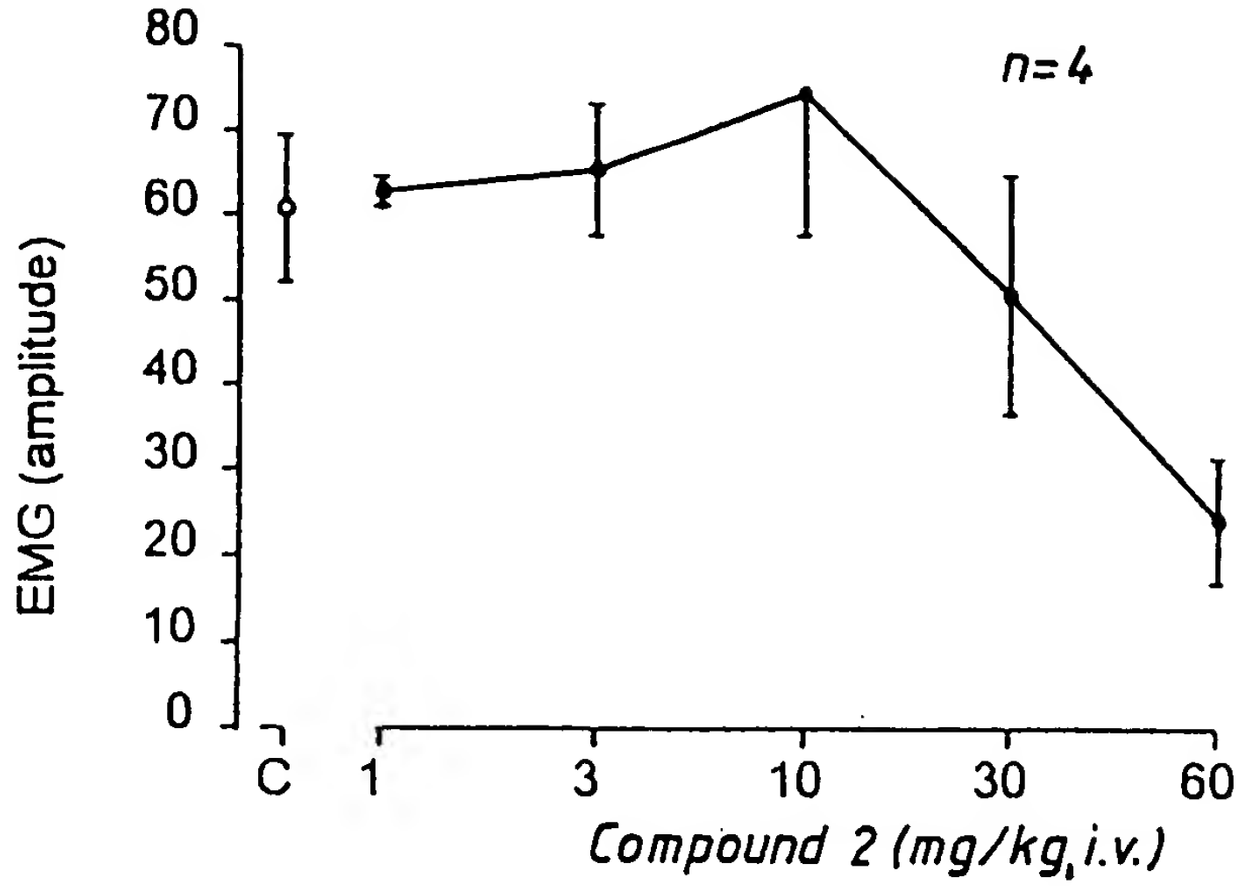
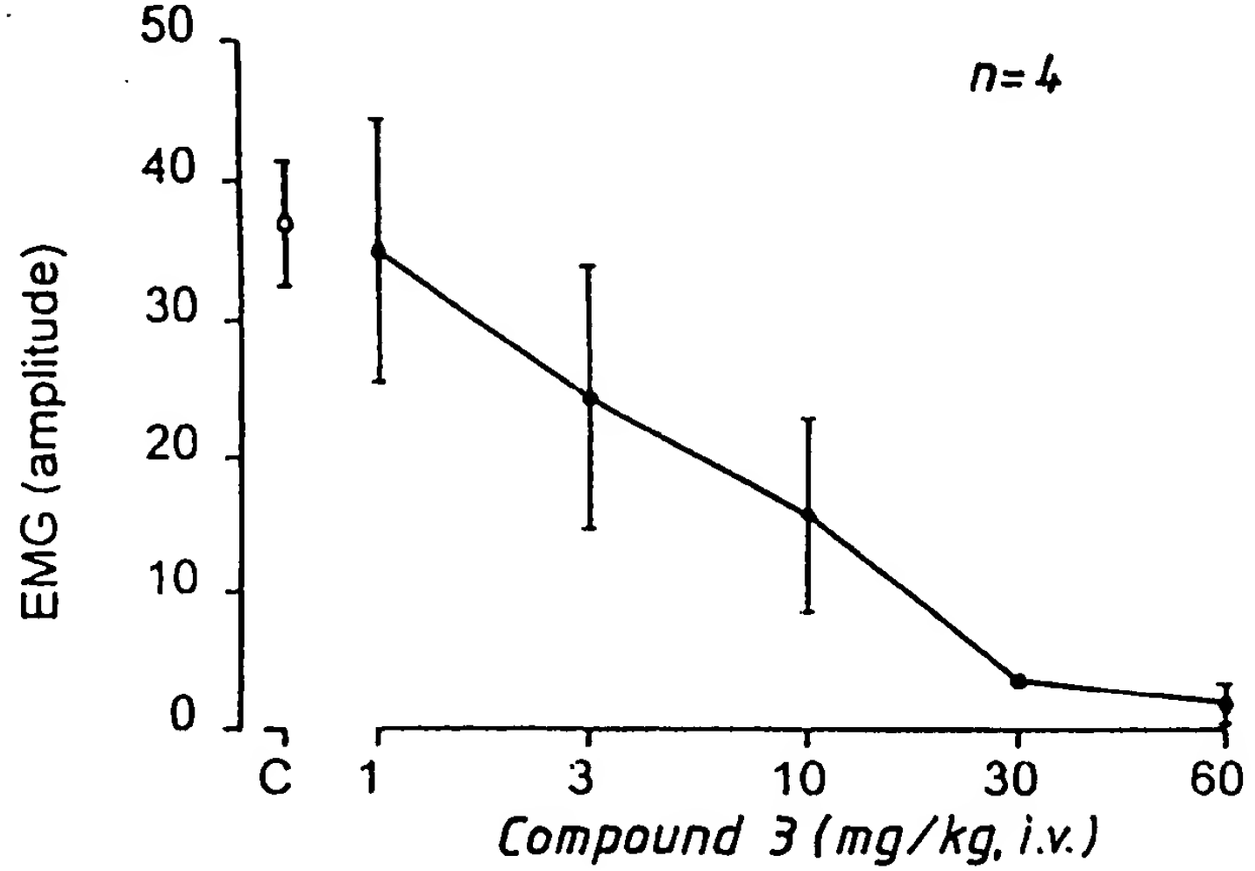

% control
n = 4
EMG amplitude
140
120
100
80
60
40
20
0
C
1
3
6
10
% control
EMG AUC
140
120
100
80
60
40
20
0
C
1
3
6
10
Memantine (mg/kg, i.v.)

Fig. 2


EMG (amplitude)
80
70
60
50
40
30
20
10
0
n=4
C
1
3
10
30
60
100
EMG (AUC)
6
5
4
3
2
1
0
C
1
3
10
30
60
100
memantine (nmol, i.t.)


n=3
EMG (amplitude)
80
70
60
50
40
30
20
10
0
C
1
3
10
30
Compound 1 (mg/kg, i.v.)


n=4
EMG (amplitude)
80
70
60
50
40
30
20
10
0
C
1
3
10
30
60
Compound 2 (mg/kg, i.v.)


n=4
EMG (amplitude)
50
40
30
20
10
0
C
1
3
10
30
60
Compound 3 (mg/kg, i.v.)

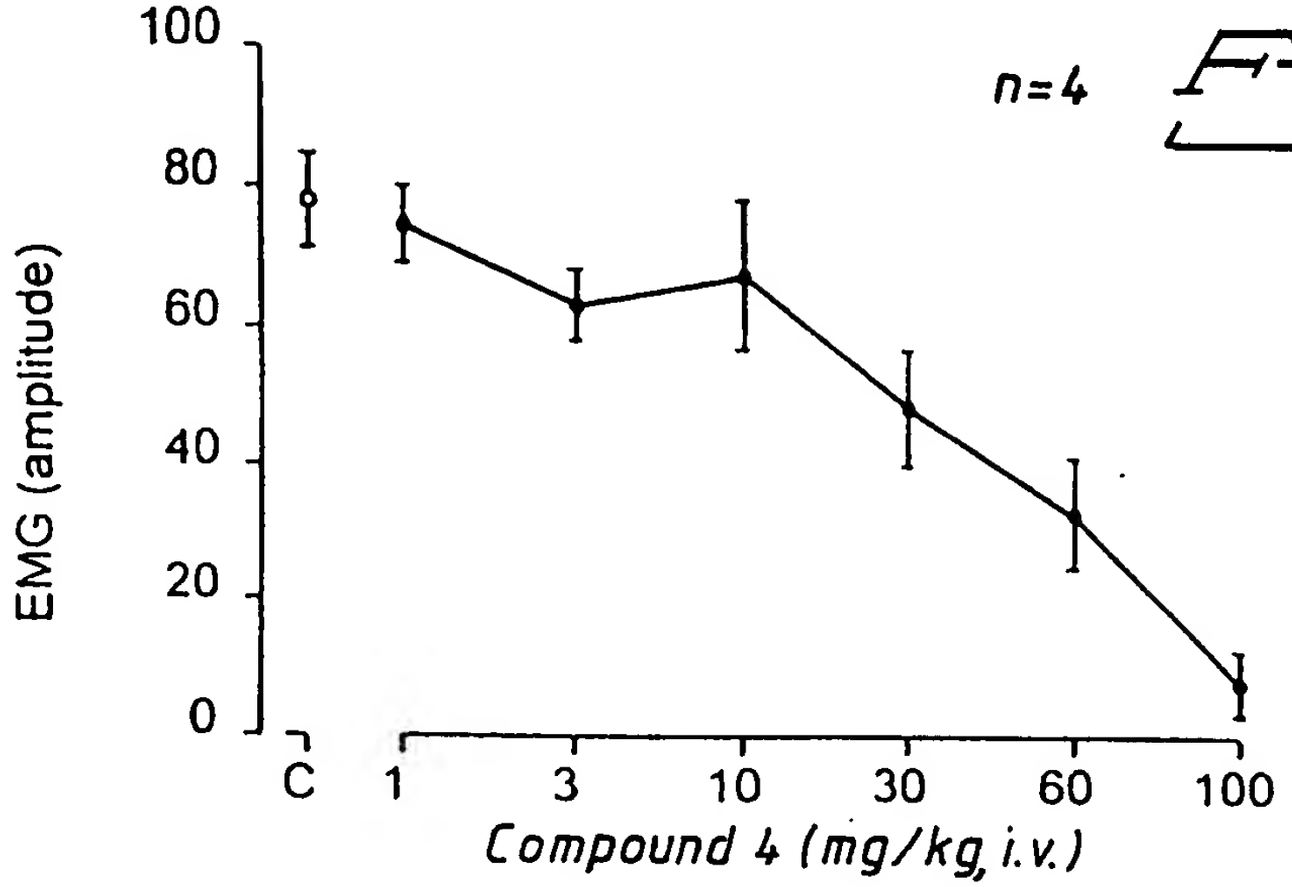

n=4
EMG (amplitude)
100
80
60
40
20
0
C
1
3
10
30
60
100
Compound 4 (mg/kg, i.v.)

Fig.3

Fig. 4

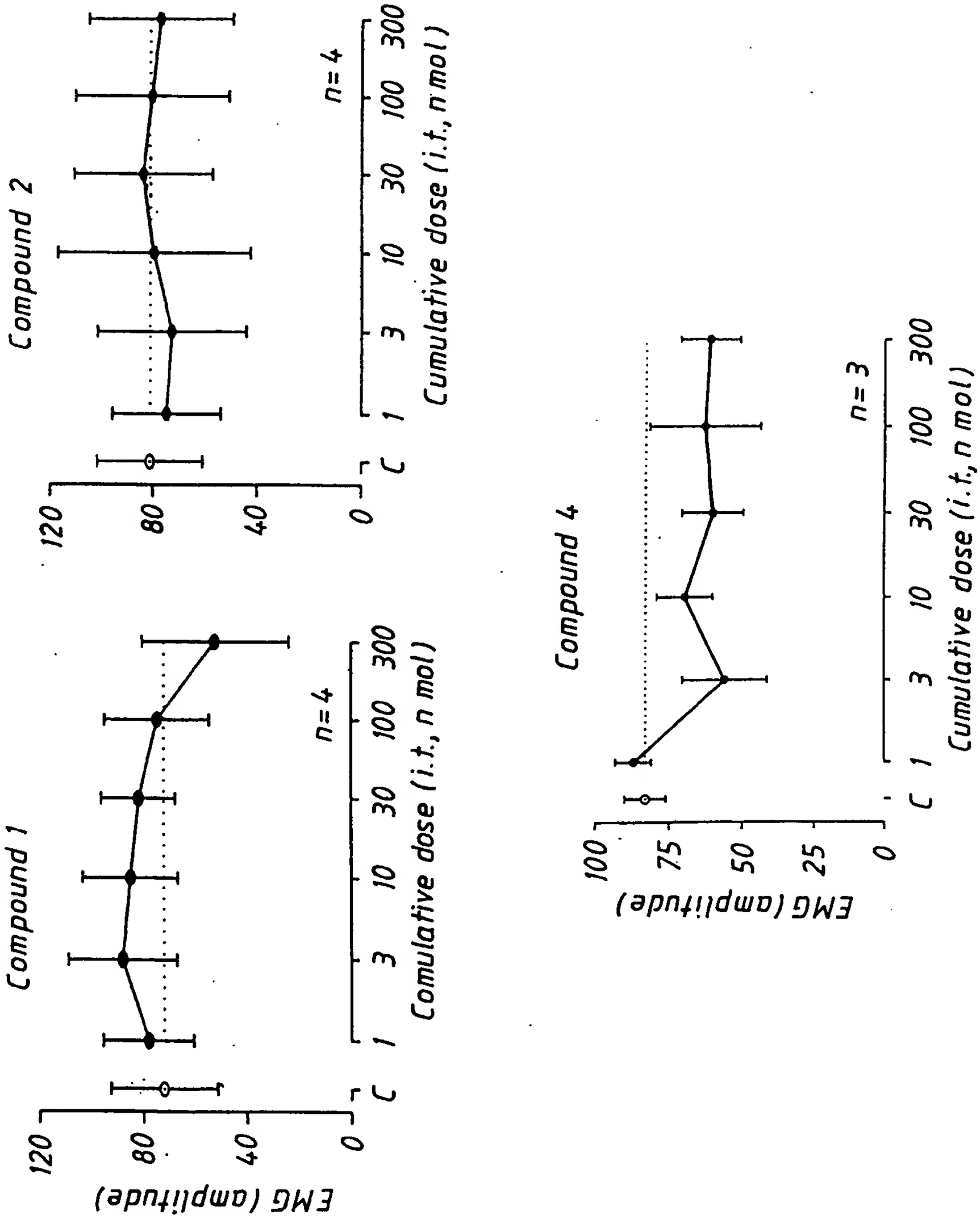

Compound 1
Compound 2
Compound 4
EMG (amplitude)
120
80
40
0
C
1
3
10
30
100
300
n=4
n=3
Cumulative dose (i.t., n mol)
Comulative dose (i.t., n mol)

Fig.5

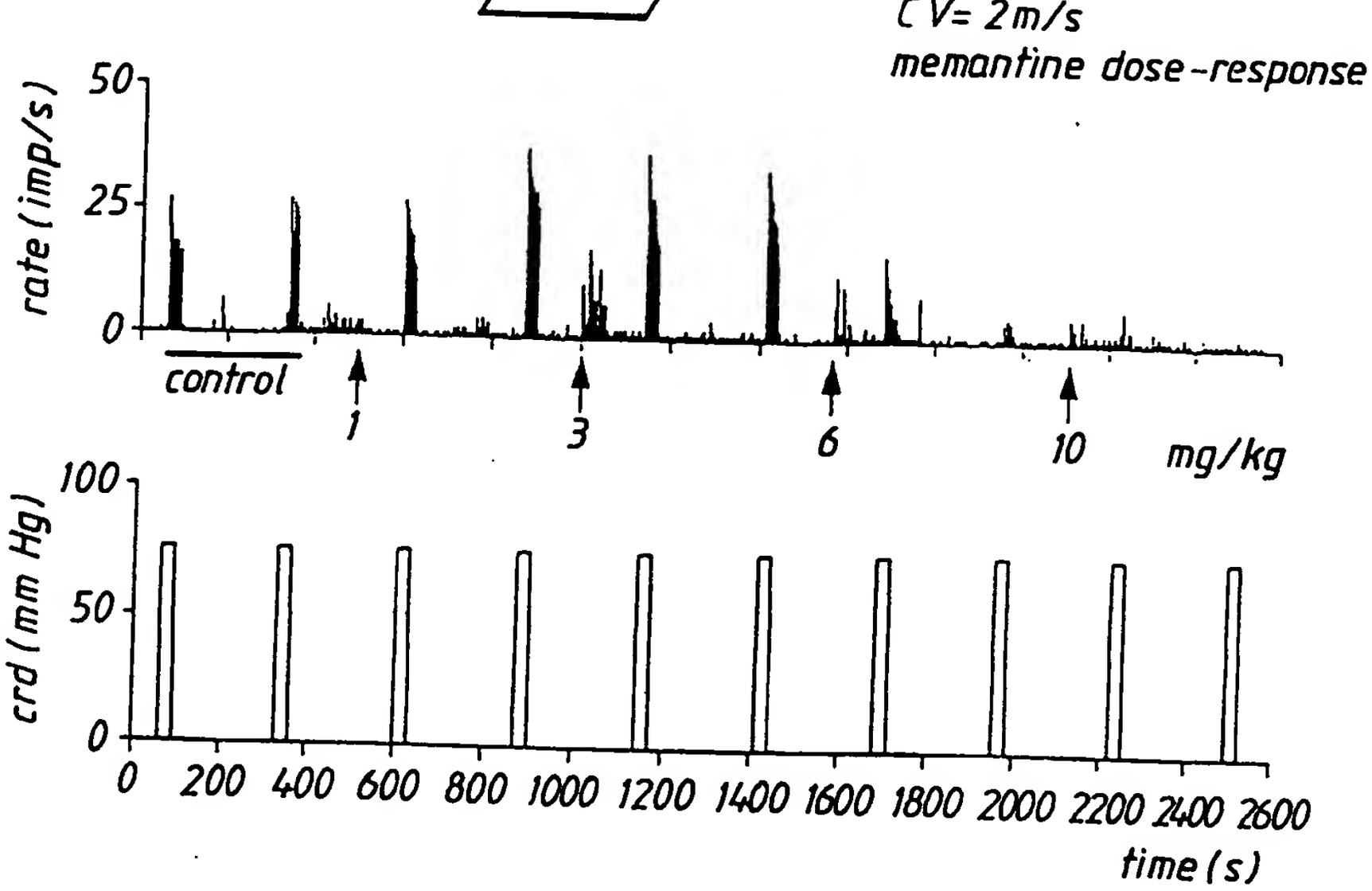
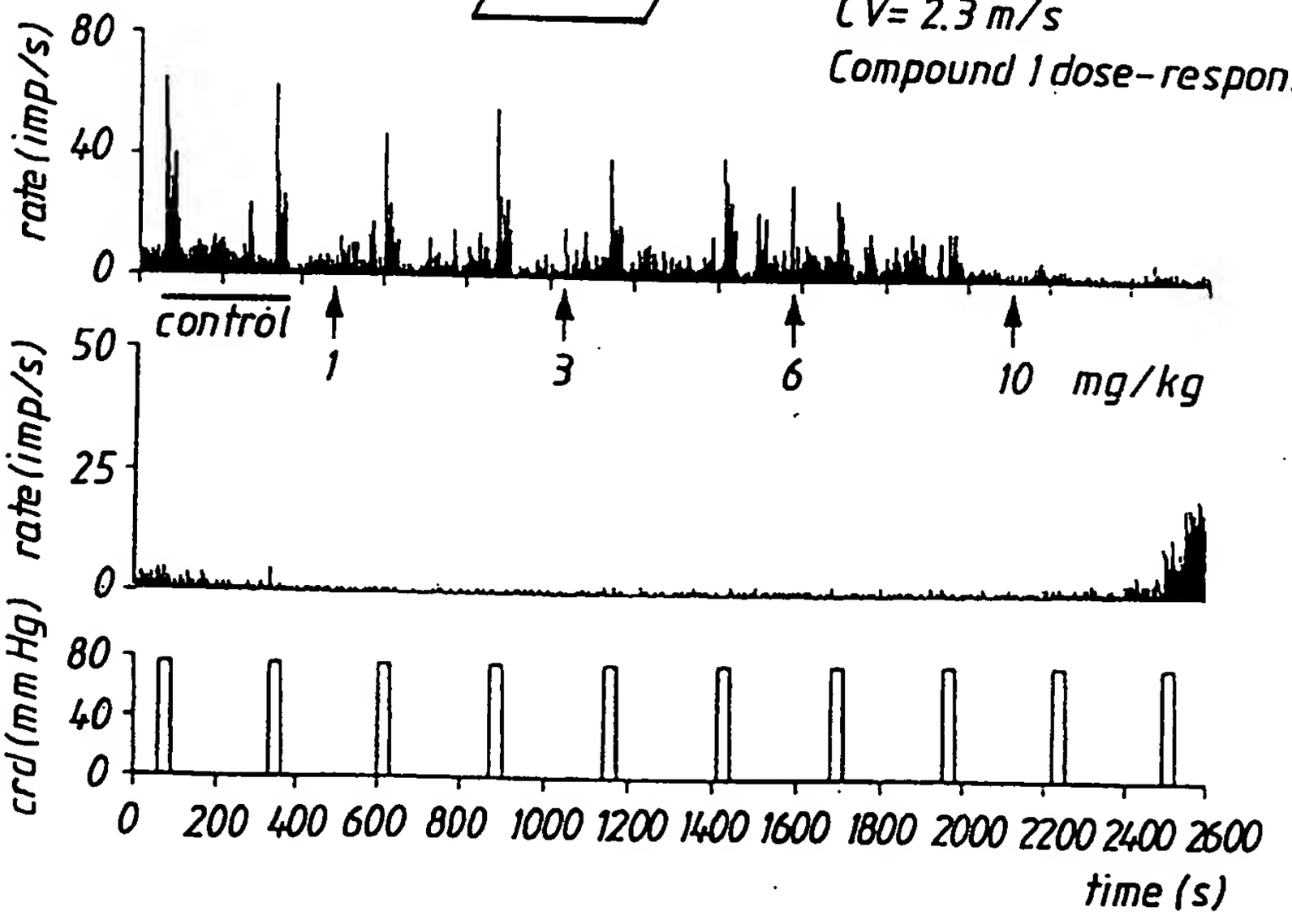

CV= 2m/s
memantine dose-response
rate (imp/s)
50
25
0
control
1
3
6
10
mg/kg
crd (mm Hg)
100
50
0
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600
time (s)

Fig.6


CV= 2.3 m/s
Compound 1 dose-response
rate (imp/s)
80
40
0
control
1
3
6
10
mg/kg
rate (imp/s)
50
25
0
crd (mm Hg)
80
40
0
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600
time (s)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00702

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/165, A61K 31/13, A61K 31/41, A61K 31/44, A61K 31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9709317 A2 (GLAXO GROUP LIMITED), 13 March 1997 (13.03.97) ---	1-2
X	WO 9714415 A1 (F.H. FAULDING & CO. LIMITED), 24 April 1997 (24.04.97) --- --------	10-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 Sept 1999	07 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00702

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☒ Claims Nos.: 1-2, 9, 10-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00702

BOX I 1.

Claim9 relates to a method of treatment of the human or animal body by surgery or by therapy practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

BOX I 2.

Present claims 1-2, 9 and 10-11 relate to a compound/method defined by reference to desirable characteristic, namely NMDA antagonist activity or sodium antagonist activity. The claims cover all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and /or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the applications so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been limited mainly to those compounds mentioned in the claims or the description.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/SE 99/00702

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9709317 A2	13/03/97	AP 640 A	14/04/98
		AP 9600857 D	00/00/00
		AU 6986596 A	27/03/97
		BG 102342 A	30/09/98
		CA 2230362 A	13/03/97
		CN 1200729 A	02/12/98
		CZ 9800655 A	15/07/98
		EP 0879230 A	25/11/98
		GB 9518027 D	00/00/00
		HR 960399 A	30/04/98
		IL 123414 D	00/00/00
		NO 980923 A	04/05/98
		NZ 318390 A	25/02/99
		PL 325329 A	20/07/98
		SK 28598 A	09/09/98
WO 9714415 A1	24/04/97	AU 7207896 A	07/05/97
		AU PN605795 D	00/00/00
		EP 0858334 A	19/08/98